University of North Carolina-Chapel Hill
Consent to Participate in a Research Study
Adult Subjects

Medical IRB Study # 00-CEMLB-476
Consent Form Version Date: **July 28, 2006**

Title of Study: Physiological Changes in Healthy Young Adults Exposed to Concentrated Chapel Hill Ambient Air Particles and Nitrogen Oxides

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UNC-CH Department: Human Studies Division of US EPA

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Sponsor: United States Environmental Protection Agency

You are being asked to take part in a research study. The investigators listed above are in charge of the study; other professional persons may help them or act for them.

What are some general things you should know about research studies?

Research studies are designed to gain scientific knowledge that may help other people in the future. You may or may not receive any direct benefit from participating. There may also be risks associated with participating in research studies.

Your participation is voluntary. You may refuse to participate, or may withdraw your consent to participate in any study at any time, and for any reason, without jeopardizing your future care at this institution or your relationship with your doctor. If you are a patient with an illness, you do not have to participate in research in order to receive treatment.

Details about this particular study are discussed below. It is important that you understand this information so that you can decide in a free and informed manner whether you want to participate. You will be given a copy of this consent form. You are urged to ask the investigators named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study? The purpose of this research study is to determine if people exposed to fine particles and to nitrogen oxides normally present in the outdoor air develop temporary changes in their lungs or heart. The levels of pollutants (particles or nitrogen dioxide) to which you will be exposed will not be higher than what you could be exposed to in major U.S. cities such as Los Angeles or New York during the traffic hours.

How many subjects will participate in this study? If you decide to participate, you will be one of the possible 40 subjects in this research study.

How long will your participation last? There will be a total of 3 visits separated by at least 4 weeks. Each visit consists of one exposure session. Before your first exposure session you will need to come to the Human Studies Facility for a training session of about an hour to get you familiarized with our facility. For all three exposure sessions you will need to be at the Human Studies Facility for approximately 3-4 hours, including 2 hours in the exposure chamber itself. You will then return to the EPA facility the morning following the exposure session for a brief follow-up exam and bronchoscopy, which will take about four hours. However, you have participated in other exposure research studies at EPA and have had exposure to filtered air, you do not need to have filtered air exposure again for this research study. That means that you will only have 2 visits.

What will happen if you take part in the study?

During the course of this study, the following will occur:

You will be given a physical examination to determine if you are eligible to participate in this study. This study requires that you have no significant problems with your nose, throat, heart, lungs or blood.

During the training session you will be practicing the different lung function tests used in this study (spirometry and diffusing capacity). In addition you will exercise on a bicycle ergometer, which helps us to determine your workload for the exposure session.

You will be reminded by telephone a few days before the exposure session. The day before exposure until the day following exposure you are asked to refrain from alcohol and from any activities where you could be exposed to high levels of pollutants (e.g. cigarette smoke or solvents). Please report any pollutant exposure to the study personnel so you can be rescheduled if necessary.

On the day of exposure, you will report to the medical station next to the guard's desk in the Human Studies Facility where the nurses will take your temperature and ask questions about any symptoms or recent acute illnesses. You will be rescheduled if you have experienced an upper or lower respiratory tract illness within the past 4 weeks, or any other acute illness within the past week. Women will be asked about their latest menstruation and a pregnancy test will be conducted. In case you are likely to be pregnant your participation will be terminated and you will receive full compensation for the exposure day. The nurses will attach electrocardiograph (ECG) leads to your chest and to a small portable recording device called a Holter monitor to

obtain a before-exposure reading of your heart rate and function. As part of this procedure you will be asked to recline quietly for 25 minutes and to breathe at a rate given by a metronome while a measurement of your heart rate is taken. The ECG leads will remain attached to allow us to monitor your heart during the exposure session. At this time you will also be asked to blow into a tube to check baseline lung function and a blood sample (75ml) will be taken from a vein in your arm.

You will then enter the exposure chamber (4 x 4 x 6 feet in size). During your first visit, you will be assigned to one of the following two protocols:

1. Clean air, air containing fine particles, air containing fine particles and nitrogen dioxide

Or

2. Clean air, air containing nitrogen dioxide, air containing fine particles and nitrogen dioxide

During each visit, you will only be exposed for 2 hours to one of the air mixtures in the protocol. We will not tell you to which of these conditions you will be exposed. You will then exercise intermittently at a moderate level on a bicycle ergometer. The schedule of exercise will be 15 minutes of exercise alternating with 15 minutes of rest for a total exercise time of 1 hour during the two-hour exposure. A physician or a trained investigator will be seated outside the chamber and be observing you at all times. A physician will be on call in the facility during the entire exposure session. During the exposure, your heart will be monitored and the amount of oxygen present in your blood will be monitored by placing a harmless device (pulse oximeter) on your finger. If it appears you are experiencing significant breathing or heart problems, or have severe headache, nausea or vomiting, or develop fever, the exposure will be terminated immediately.

Immediately after the exposure you will again blow into a tube to determine if the exposure caused changes in your lung function. Then you will again recline quietly for 25 minutes while your heart rate is measured. Then a blood sample will be taken. Finally you will exercise on a bicycle ergometer and then again blow into a tube to measure your lung function.

The next morning your will return to the EPA facility. This follow-up should take about four hours of your time. The nurses will check you in and a physician will ask if you encountered any difficulties. The lung function and heart measurements will be repeated, and another blood sample will be taken.

Finally bronchoscopy will be done for a bronchoalveolar lavage (washing of areas of the lung). For this purpose, a bronchoscope (similar to a thin tube) will be inserted through your nose and passed through the back of your throat to reach the trachea (windpipe) and the airways leading to the lungs. To reduce coughing and discomfort you will gargle and inhale an anesthetic (topical lidocaine) prior to beginning the procedure. Saline will be released and recovered through the bronchoscope to wash that part of the lungs. This washing procedure will be repeated up to 6 times on each side of the lung. It is essential that you (1) take nothing by mouth after midnight before bronchoscopy, (2) take nothing by mouth for two hours after the procedure, (3) stay for a

suitable observation period after the procedure at the discretion of the physician involved and not ride a bicycle or motorcycle home. Prior to bronchoscopy, a small tube will be placed in a vein for potential use in administering fluids. Immediately before the bronchoscopy you may be given an intravenous injection of atropine in your arm to control coughing and decrease salivation if the physician considers it necessary. The medication can cause some increase in heart rate and a dry mouth. During the procedure you will receive cardiac monitoring and supplemental oxygen. You will be closely monitored and if adverse reactions occur, prompt corrective action will be initiated. After the bronchoscopy, you will recover in the recovery area. A nurse will check with you frequently for any discomfort. When you can drink fluids without any swallowing difficulty, you will be discharged from the facility. A discharge sheet containing physician's contact information will be given to you upon discharge so that you can contact one of our physicians if you have any questions.

Are there any reasons you should not participate? You should not participate in this study if you are unhealthy or pregnant. You need to be non-smoker for at least 1 year prior to the study and have smoked not or only little earlier in life. There are several medical conditions that may prevent you from participating in this study. These include, but are not limited to, regular use of medications including over the counter medication (except for birth control pills and low dose antibiotics for acne), active allergies, diabetes, need for a pacemaker, heart attack or coronary bypass surgery ever before, dialysis treatment, and need for supplemental oxygen. The physician and nursing staff will explain other potential exclusionary conditions in detail to you.

What are the possible risks or discomforts?

This study might involve the following risks and/or discomforts to you:

If you have any tendency to become uncomfortable in small closed spaces, it is possible that you may become uncomfortable during this study. You will be taken to the exposure chamber when you are first evaluated for suitability for the study to allow you an opportunity to see where you will sit and what the chamber looks like.

You will be exposed to fine particles concentrated from Chapel Hill air. Some studies suggest that elderly people, particularly those with underlying cardiovascular disease, may be at increased risk for developing illness or even dying as a result of exposure to fine particles. However, the risk for young healthy people is minimal. At this time, no one understands exactly how particles might cause increased mortality or morbidity. While we cannot exclude the possibility that you may have an adverse reaction to breathing these particles, you will only be exposed to them for a 2 hour period, and they will not exceed levels to which you would be exposed if you visited a major metropolitan area such as Los Angeles or New York for 2 hours on a smoggy day.

You will be exposed to nitrogen dioxide given alone or at the same time with fine particles. The concentration of nitrogen dioxide used in this study (0.5 parts per million, ppm) is low. At high concentrations (> 10 ppm), nitrogen dioxide might cause cough, shortness of breath, breathing discomfort, or even a slight headache. These symptoms will typically disappear within a few hours but may last longer if you are especially sensitive. Nitrogen dioxide might also

temporarily injure some of the cells lining your airways; the effects of this are not thought to be permanent or harmful. There may also be a slightly increased chance of catching a cold following exposure to nitrogen dioxide. Based on current knowledge, a single exposure to nitrogen dioxide will not have any permanent adverse health effects at the concentration being used in this experiment.

Because nitrogen dioxide will be given with fine particles, there is a possibility that you will experience more and stronger symptoms than you would experience when exposed to fine particles or nitrogen dioxide alone, a question that is being tested by this protocol. Experience from tunnel construction worker that are exposed every working day to much higher concentrations of a combination of these pollutants suggest that after several years of exposure the likelihood for chronic lung diseases will be increased. Since you will be exposed only for two hours to concentrations that can be found on smoggy days at roadsides of major US-cities, the combination of particles and nitrogen oxides should not have any permanent adverse health effects at the concentrations being used in this experiment.

To ensure your safety, concentrations of nitrogen dioxide in the chamber will be monitored continuously. A gas delivery system maintains a stable concentration of nitrogen oxides inside the chamber, and concentrations are expected to vary by less than 10%. An alarm will go off if the concentration in the chamber exceeds the desired concentration by more than 10%. The gas delivery system will be shut down automatically if the concentration goes 20% above the desired concentration (0.5 ppm nitrogen dioxide). Also if the particle concentration in the chamber exceeds 500 $\mu g/m^3$, we will not conduct particle exposure study.

There are no risks associated with the lung function measurements in which you blow through a tube. One of the lung function tests requires that you inhale a gas mixture containing 0.3% CO, 0.3% methane and 0.3% acetylene. Inhalation of high concentrations of CO over several minutes may cause headache, nausea, and dizziness. Methane is an inert gas and has small effects even at high concentrations. Acetylene is a gas that at high concentrations may cause headache and dizziness. The concentrations of the gas mixture you will inhale are moderate and you will inhale them only for a very short time. The inhalation will be stopped immediately should you develop any of the following symptoms: headache, nausea, dizziness or general discomfort.

There are no risks associated with monitoring your heart by ECG or blood oxygen by pulse oximetry. However, preparing your skin for placement of ECG electrodes and removing the electrodes the next day may cause some irritation, itching, or burning in some people. If this occurs you should call the nursing staff. The risks associated with taking venous blood samples are considered minimal. Blood samples will be taken by a licensed nurse. There are several risks associated with performing bronchoscopy, although these risks are exceedingly small when bronchoscopy is performed on young healthy subjects. The primary risk of bronchoscopy is coughing and discomfort in the nose and throat, which is caused by having the bronchoscope inserted through the nose and passed through your throat. This discomfort and coughing is alleviated with topical lidocaine, which you will gargle and inhale prior to the beginning of the procedure. If you are unable to tolerate the passage of the bronchoscope through your nose and throat because of pain or uncontrollable coughing in spite of having received the maximum

allowable amount of lidocaine, the procedure will be immediately terminated.

On very rare occasions, bronchoscopy can cause an asthmatic attack, characterized by wheezing, chest tightness, and shortness of breath. This type of complication is very, very rare in subjects who have no history of asthma or other lung diseases. If an asthma attack occurs, the bronchoscope will be removed, and inhaled medication used to treat asthma (e.g., albuterol) will be given. These steps are usually all that is necessary to terminate the attack. However, if further care is needed, you will be transferred by ambulance to the Emergency Room at University of North Carolina Hospital.

Bleeding from the nose can also occur as a result from bronchoscopy. It is usually caused by rubbing of the bronchoscope against the inside of the nose. This type of bleeding is almost always very minor, causing streaking of the nasal mucus, which resolves spontaneously within an hour or so after completion of the bronchoscopy. On extremely rare occasions, moderate to severe nose bleeding would require packing your nose with sterile gauze and transferring you to the Emergency Room at University of North Carolina Hospital. Aspirin products (including BC Powders or Goodys Powders) and anti-inflammatory medications such as Motrin (ibuprofen) and Naprosyn (naproxen) may cause an increased tendency to bleeding. It is essential that you not take these types of medications for at least three days prior to bronchoscopy (acetaminophen [Tylenol] is acceptable).

Another risk that can occur from performing bronchoscopy is pneumothorax (collapsed lung). This usually only occurs when biopsies (tissue samples) are being done in the outer part of the lung. We will not take biopsies and the bronchoscope will remain in the large central airways. In the very unlikely event that a pneumothorax does occur, you must be aware of the symptoms that it can cause: chest pain and shortness of breath. If these symptoms do occur after your bronchoscopy, you must contact the EPA medical station immediately (966-6232), or you must contact the physician who performed the bronchoscopy. His name and telephone number are on the discharge sheet you were given when you left the facility. If pneumothorax occurs after bronchoscopy, it usually occurs within 24 to 48 hours after the procedure is complete. The lidocaine used for anesthesia during the procedure can have some adverse effects because some of the lidocaine can be absorbed into the blood stream from the nose and the lungs. If you are allergic to lidocaine, you could develop itching, hives, difficulty breathing, and possibly shock (a dangerous drop in blood pressure). This risk is minimal, but you will be excluded from the study if you are allergic to lidocaine or any other topical anesthetic that is commonly used in minor surgical or dental procedures. Lidocaine can also cause symptoms in your central nervous system (confusion, tremor, euphoria, or, rarely, seizure) or heart rate disturbances (very fast or very slow heart rate) if an excessive dose of medication is used. Finally a death in a volunteer receiving an overdose (over 1000 milligrams) of lidocaine during bronchoscopy has been reported from Rochester, New York. However, no serious side effects of this medication have been noted at lower doses such as those described in this protocol, which usually does not exceed 300 milligrams of lidocaine during the entire procedure. If any problems develop secondary to the use of lidocaine, Dr. Ghio or the physician on duty that day at the Human Studies Division of the EPA will be available to handle these problems.

Atropine, the medication given to you by vein before the bronchoscopy procedure starts, is given to help prevent your blood pressure and pulse from falling when the bronchoscope is first put into your airway, and to reduce the amount of secretions present in your nose, throat, and airway during the procedure. Atropine can cause you to have a dry mouth and nose as well as an increased pulse for about 30 to 60 minutes after it is given. These side effects are not harmful to you, and they wear off within 30 to 60 minutes after the drug is given.

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The placement of an IV catheter in your arm can cause some pain. However, the IV is placed by a physician assistant or nurse who is very experienced in this technique, and the pain is very minor, usually resolving very soon after the IV catheter is in place. Rarely, placement of an IV catheter can result in the formation of a hematoma (bruise) at the site of the IV after it is removed. Also, a rare complication of IV placement is skin infection or an infection of the vein in which the IV catheter has been placed. The risk of getting an infection from the IV is minimized by the nurse's use of sterile technique to place the catheter. If you do have signs of infection at the IV site (redness, warmth, painful skin, swelling) after completion of the procedure, you will need to contact the EPA medical station (966-6232) or the physician who performed the bronchoscopy. You are not at increased risk by having blood drawn through the IV catheter.

Some subjects who undergo bronchoscopy may have a low-grade fever (less than 101 degrees Fahrenheit) after the procedure is completed. This fever is almost always benign, and it occurs in approximately 25 percent of all subjects who undergo bronchoscopy. This fever usually resolves within 24 hours with the use of Tylenol. Nevertheless, a persistent fever or any temperature of greater than 101 degrees Fahrenheit might mean that you have an infection, particularly pneumonia. Therefore, if you have any fever greater than 101 degree Fahrenheit after the bronchoscopy or a fever that doesn't resolve in 24 hours after the procedure is completed, you should contact the EPA medical station or the physician who performed the bronchoscopy so that arrangements can be made for you to be examined by one of the physicians at EPA.

Finally there is a small possibility (less than 1 percent) that you might get pneumonia as a result of bronchoscopy in which bronchoalveolar lavage is performed. The signs and symptoms of pneumonia include: 1) fever greater than 101 degrees Fahrenheit or persistent fever, 2) persistent cough with or without sputum production, 3) chest pain, 4) shortness of breath with exercise or at rest, 5) coughing up of blood. If you experience any of these symptoms after bronchoscopy, you must contact the EPA medical station or the physician who performed the bronchoscopy so that arrangements can be made for your examination by an EPA physician. You will be contacted 24 to 48 hours after the bronchoscopy to see if you are experiencing any of the above mentioned. In addition, there may be uncommon or previously unrecognized risks that might occur.

<u>What are the possible benefits</u>? The possible benefits to you of participating in this study may be a complete medical examination that includes blood work, lung function testing, and baseline

ECG at no charge. However, this is not a substitute for a routine doctor visit. The medical staff will explain to you any remarkable findings regarding your overall health status. In addition, if we observe changes in your heart rate or lungs as a consequence of exposure to air pollutants, you may elect to use this information to avoid exposure on high pollution days. The primary benefit to society produced by this study will be a better understanding of whether or how air pollution particles and nitrogen oxides affect people. Given that every member of American society is currently exposed to these pollutants, this study has the potential to contribute to devising effective strategies aimed at protecting millions from the untoward effects of these particles.

What if we learn about new risks during the study? You will be given any new information gained during the course of the study that might affect our willingness to continue your participation.

How will your privacy be protected? No subjects will be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-CH will take all steps allowable by law to protect the privacy of personal information.

Will you be paid for participating? You will receive up to $2139.00 for your participation in this study if you complete all three exposure sessions. The reimbursement is itemized below:

Pre-study Qualifications	
Screening	$15
Physical Exam	$15
Exposure Session (3 exposures, 2 hrs per exposure at $36/hr)	$216
Training (1hr), check-in, pre-testing and post-testing (4hrs x 3 = 12 hrs), day-after-exposure testing (2hr x 3 = 6 hrs) at $12/hr	$228
Pulmonary function tests with DLCO (at $40 each x 6)	$240
24 hour Holter monitor (at $100 each x 3)	$300
Bronchoscopy with lavage and recovery (at $325 each x 3)	$1075
Completion bonus	$50
Total Compensation	$2139

The compensation for this study does not include parking costs at the UNC campus which will be reimbursed separately.

If you have had a filtered air exposure from previous EPA exposure studies, you will only need 2 exposures for this research study. Therefore, you will be paid for participating in 2 sessions. In this case, the total payment will be $1356.

Exposure Session (2 exposures, 2 hrs per exposure at $36/hr)	$144
Training (1hr), check-in, pre-testing and post-testing (4hrs x 2 = 8 hrs), day-after-exposure testing (2hr x 2 = 4 hrs) at $12/hr	$152
Pulmonary function tests with DLCO (at $40 each x 4)	$160
24 hour Holter monitor (at $100 each x 2)	$200

Bronchoscopy with lavage and recovery (at $325 each x 2)	$650
Completion bonus	$50
Total Compensation	$1356

Will it cost you anything to participate? The U.S. EPA will pay the costs of this research. You will not be billed for any procedures. However, if you are deemed not eligible to participate in the study for medical reasons, we may recommend that you seek follow up care from your own health care provider for abnormalities discovered during the screening history and physical examination. Such care is entirely at your own expense. EPA will not provide reimbursement for any follow up care.

What will happen if you are injured by this research? All types of research involve possible risk, some including the risk of personal injury. In spite of all precautions, you might develop complications from participating in this study. If such complications arise, the researchers will assist you in obtaining appropriate medical treatment, but any costs associated with the treatment will be billed to you and/or your insurance company. Neither the University of North Carolina at Chapel Hill nor the US EPA has not set aside funds to compensate you for any such complications or injuries, or for related medical care. However, by signing this form, you do not waive any of your legal rights.

If you believe you have suffered research-related injury, you have the right to pursue legal remedy if you believe that your injury justifies such action. The Federal Tort Claims Act, 28 U.S.C. " 2671, et seq., provides for money damages against the United States when property loss or personal injury results from the negligent or wrongful act or omission of any employee of the EPA while acting within the scope of his or her employment. Signing this consent form does not waive any of your legal rights or release the investigator, the sponsor, the institution or its agents from liability for negligence. If a research-related injury occurs you should contact the Director of EPA's NHEERL Human Research Protocol Office at 919-966-6217.

What if you want to stop before your part in the study is complete? You understand that your participation is voluntary. You may terminate your participation in the study at any time without penalty, and without losing benefits you would otherwise be entitled to. If you elect to terminate your participation in the study, you will be paid for that portion of the study, which has been completed, but will be ineligible for further participation in the study and any payments you would have received for future participation. If, however, we elect to terminate an exposure session for any reason, you will be paid up to the portion of the study that you have participated. The investigators also have the right to stop your participation if the entire study has been stopped. If this occurs, you will be paid for the entire study.

What if you have questions about this study? You have the right to ask, and have answered, any questions you may have about this research. If you have further questions, or if a research-related njury occurs, you should call one of the listed investigators:

Andy Ghio, M.D. 919-966-0670
Robert Devlin, Ph.D. 919-966-6255

Or the Director of the NHEERL Human Research Protocol Office:

Richard Hermann, M.D. 919-966-6217

What if you have questions about your rights as a subject?

This research has been reviewed and approved by the Committee on the Protection of the Rights of Human Subjects (Medical IRB) at the University of North Carolina at Chapel Hill. If you have any questions or concerns regarding your rights as a research subject, you may contact the Chairman of the Committee at (919) 966-1344 and the Director of the NHEERL Human Research Protocol Office at (919) 966-6217.

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Subject's Agreement:

I have read the information provided above. I voluntarily agree to participate in this study.

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Signature of Research Subject Date

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Printed Name of Research Subject

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Signature of Person Obtaining Consent Date

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Printed Name of Person Obtaining Consent